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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,753	09/14/2005	Roger Kenneth Smith	2985-1-001	6929

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,753	SMITH ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 19-40* is/are pending in the application.

4a) Of the above claim(s) *19 and 24-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,20-23 and 34-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 1-17,20,20-23 and 34-40 in the reply filed on 04/06/2009 is acknowledged.

The species election requirement is hereby withdrawn.

Claims 1-17,19-40 are pending. Claims 19 and 24-33 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 04/06/2009. Claims 1-17,20-23 and 34-40 are under consideration in the instant office action.

Claim Objections

Claim 24 is objected to because of the following informalities: Claim 24, at line 3, reads "compared to a natural source the" and should read "compare to a natural source *of* the". Appropriate correction is required.

Claim 34 is objected to as it depends from a withdrawn claim. Claim 34 should be written in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of enablement

Claims 1-16,20-23 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method using cell isolated from bone marrow aspirate, does not reasonably provide enablement for the claimed method using a composition of mesenchymal stem cells. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The invention relates to use of cells isolated from bone marrow, expansion of said cells in culture, and introducing the expanded cells into a tendon injury of an injury to cause healing.

The claims specifically recite the use of mesenchymal stem cells in the claimed method. The specification teaches only separation of bone marrow aspirate over a Ficoll gradient, isolating a fraction of cells of unknown character and composition, and culturing/expanding said cells in the presence of DMEM. However, the specification does not characterize the cells isolated in the fractionation method in any manner to demonstrate the presence of mesenchymal stem cells, much less determining the effective concentration for tendon repair and/or regeneration. The specification only teaches quantitation of the cells in the heterogeneous population and fails to identify any cell types (page 18). The specification states that a weakness of the prior art lies in a lack of describing the presence and number of mesenchymal stem cells in aspirated bone marrow prior to use in injury treatment. The specification states "Some clinicians have thus doubted the efficacy of this technique as smears of aspirate bone marrow resemble peripheral blood smears" (page 2). While the specification teaches expansion of cells isolated from bone marrow aspirate, this step is not required by the claims. Furthermore, the presence of mesenchymal stem cells, even after expansion, has yet to be confirmed. Thus, the specification fails to

support that use of mesenchymal stem cells, as opposed to a heterogenous population o f unidentified cells isolated from bone marrow, will result in treatment of soft skeletal tissue injury.

Enablement

Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In addition to the issues present above, claim 17 fails to be enabled for any claimed breadth. Claim 17 is drawn to the claimed method of treatment of claim 1, requiring administration of MSC cells to a soft skeletal injury to cause treatment. Claim 17, additionally, requires one or more growth factors to be present in the composition to encourage differentiation of MSCs into tenocytes. While the specification prophetically describes such methodology, the specification fails to provide guidance with respect to what growth and/or differentiation factors will achieve this goal. At the the time of filing it was well-known that different growth factors had different effects on various types of stem cells. These effects were also known to be variable between species. For example, Caplan (2001, IDS) taught that dexamethoasone directs hMSCs along the osteogenic path while it induces mouse MSCs along an adipogenic path. Additionally, BMP2, at low doses directs mouse MSCs along an osteogenic path whereas very high doses are required to achieve the same effect on hMSCs. Thus, the responsiveness of MSCs to different growth factors can differ amongst species. Furthermore, and most importantly, different factors have different effects on the directed differentiation of MSCs in general (see page 3 of the review).

Therefore, in light of the absence of guidance in the specification with respect to which factors can achieve the claimed effect, and in light of the teachings in the art that different factors have different effects on the directed differentiation of stem cells, it would require undue experimentation to determine

which growth factors to include in the composition to result in directed differentiation of MSCs into tenocytes in vivo.

Written Description

Claims 1-17,20-23 and 34-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims require introducing mesenchymal stem cells in a liquid suspension of bone marrow supernatant. However, the specification fails to describe what a 'bone marrow supernatant is". The specification teaches use of platelet rich plasma as a medium for introducing cells into a soft skeletal tissue injury (page 17). The specification does not support use of any "bone marrow supernatant" as claimed.

The claims broadly encompass administration of the stem cells to any site, including IV administration or to a noninjured site. The specification fails to contemplate such administration.

Claims 21 and 39 require introducing cell populations comprising particular percentages of mesenchymal stem cells. However, the specification fails to support characterization of the cell populations to demonstrate any of the claimed percentages. The specification provides no guidance or reference to how MSCs were identified and quantified.

Claim 17 requires including one or more growth factors that encourage differentiation o f MSCs into tenocytes. The specification fails to describe which growth factors fall into this genus. Without any mention of a single growth factor that can achieve this result, the generic recitation of the idea in the specification fails to amount to possession of the invention as claimed.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim1-17,20-23 and 34-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 34 are is incomplete as written. The preamble of the claim is directed to a method of treatment. However, the claim is incomplete because the method steps do not relate back to the preamble in a positive process. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9,12-14,16,22 are rejected under 35 U.S.C. 102(b) as being anticipated by Herthel (Nov 2001, IDS).

Herthel taught removal of 20-30ml of bone marrow aspirate from the sternum of a horse and subsequent injection of a portion (less than 6ml) to a suspensory ligament injury (strain induced injury). The aspirate is considered to comprise "bone marrow supernatant" and is a liquid suspension as claimed. Because the bone marrow aspirate is not cultured, it contains all types of bone marrow cells including mesenchymal stem cells as claimed. The transferred cells were autologous, which is also allogenic.

Claims 1-6,12-14,22, 34-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Awad (1999, IDS).

Awad taught culture and expansion of mesenchymal stem cells from bone marrow of rabbits. The cells were suspended in DMEM and a gel collagen solution (page 269). As the claimed 'bone marrow supernatant' is not defined by the specification, the collagen solution is broadly interpreted to be a bone marrow supernatant. The gel implant seeded with bone marrow stem cells was placed into patellar tendon defects of rabbits followed by suture of the overlying epitenon. The tendon defect was surgically created, which is a strain on the tendon, as claimed (claim 2). The implants used autologous cells, which are also allogenic.

Claims 1-6,12-15,21,23,34-36,39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,811,094.

'094 taught the use of autologous mesenchymal stem cells isolated from a variety of sources as a treatment for soft skeletal tissue damage, including tendon damage (col. 6) by administration of MSCs to an area of damage. '094 taught the use of humans as patients. '094 taught that MSCs are found in bone marrow, dermis, periosteum, yolk sac and the umbilical cord (column 2) and that they can be cultured and enriched at least 10^3-fold (column 12) and can be obtained as a purified homogeneous population (col. 1) prior to use. '094 taught the use of collagen gel as a carrier for the cells used in treating defects such as cartilage damage (col. 47). The specification defines liquid suspension as on which gels in situ or is mixed with another agent to cause gelling (page 9, lines 1-4). Thus, a collagen matrix constitutes a liquid suspension. As the claimed 'bone marrow supernatant' is not defined by the specification, the collagen solution is broadly interpreted to be a bone marrow supernatant.

Claims 1-7,12-14,16,21-23,34-36,39 and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,835,377 (filed 05/13/1998).

'377 taught the use of an expanded population of mesenchymal stem cells as a treatment for soft skeletal tissue damage, including tendon damage (col. 2) by administration of MSCs to an area of damage (see col. 5). '377 teaches autologous administration of cells in a collagen gel (col. 3). The gel is injected as a liquid and allowed to gel in place via arthroscopic surgery which include closing the lesion. The specification defines liquid suspension as on which gels in situ or is mixed with another agent to cause gelling (page 9, lines 1-4). Thus, a collagen matrix constitutes a liquid suspension. As the claimed 'bone marrow supernatant' is not defined by the specification, the collagen solution is broadly interpreted to be a bone marrow supernatant. '377 taught the use of humans as patients as well as dogs as models.'377 teaches culture of adherent cells which are only the desired MSCs, meeting the limitations of claims 21 and 39.

Claims 34, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,811,094 in view of Herthel (Nov 2001, IDS).

. '094 taught the use of autologous mesenchymal stem cells isolated from a variety of sources as a treatment for soft skeletal tissue damage, including tendon damage (col. 6) by administration of MSCs to an area of damage. ''094 taught that MSCs can be cultured and enriched at least 10^3-fold (column 12) and can be obtained as a purified homogeneous population (col. 1) prior to use. '094 taught the use of collagen gel as a carrier for the cells used in treating defects such as cartilage damage (col. 47). The specification defines liquid suspension as on which gels in situ or is mixed with another agent to cause gelling (page 9, lines 1-4). Thus, a collagen matrix constitutes a liquid suspension. As the claimed 'bone marrow supernatant' is not defined by the specification, the collagen solution is broadly interpreted to be a bone marrow supernatant. While '094 taught treatment of a generic tendon, it did not teach treatment of specific tendons as recited in claims 37 and 38.

However, Herthel taught the same methodology comprising administration of MSCs to treat ligament damage. More specifically, Hethel taught treatment of a suspensory ligament injury (strain induced injury).

It would have been obvious to combine the teachings of '094 with those of Herthel to arrive at the claimed method wherein the tendon treated is the SDFT. Such a combination would have been obvious because '094 taught that any ligament can be treated and Herthel taught that the SDFT is a common ligament injury in need of treatment. One would motivated to make such a combination to treat a fairly common soft tissue injury that is debilitating and in need of treatment.

Claims 34, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,835,377 (filed 05/13/1998). in view of Herthel (Nov 2001, IDS).

. '377 taught the use of an expanded population of mesenchymal stem cells as a treatment for soft skeletal tissue damage, including tendon damage (col. 2) by administration of MSCs to an area of damage (see col. 5). '377 teaches autologous administration of cells in a collagen gel (col. 3). The gel is injected as a liquid and allowed to gel in place via arthroscopic surgery which include closing the lesion. The specification defines liquid suspension as on which gels in situ or is mixed with another agent to cause gelling (page 9, lines 1-4). Thus, a collagen matrix constitutes a liquid suspension. As the claimed 'bone marrow supernatant' is not defined by the specification, the collagen solution is broadly interpreted to be a bone marrow supernatant. While '377 taught treatment of a generic tendon, it did not teach treatment of specific tendons as recited in claims 37 and 38.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632